TITLE PAGE

Full title:
New drug, new problem – do hip fracture patients taking NOACs experience delayed surgery, longer hospital stay, or poorer outcomes?

Short title:
NOAC therapy is associated with delayed surgery for hip fracture patients.

George J.M. Hourston[1], Michael P. Barrett[2], Wasim S. Khan[2], Madhavi Vindlacheruvu[2], Stephen M. McDonnell[2*]

[1]School of Clinical Medicine, University of Cambridge
[2]Department of Trauma & Orthopaedics, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, United Kingdom

*Corresponding author:
Stephen McDonnell MBBS BSc, MD FRCS Trauma & Orthopaedics
Department of Trauma & Orthopaedics
Addenbrooke's Hospital
Hills Road
Cambridge
CB2 0QQ
Email: sm2089@cam.ac.uk

Manuscript word count: 2375

ABSTRACT

Introduction

Neck of femur fractures are common in the comorbid, often anticoagulated, elderly. Non-vitamin K antagonist oral anticoagulants (NOACs) may affect patient outcomes. We aimed to evaluate whether hip fracture patients admitted on warfarin or NOAC therapy were at risk of operative delay, prolonged length of stay, or increased mortality.

Methods

We collected data for 845 patients admitted to our centre between October 2014 and December 2016. Multivariable linear regression analysis was performed to test the association between warfarin and NOAC therapy on time to surgery and length of stay. Variables in the regression model were age, sex, admission AMTS, pre-fracture mobility, ASA score, fracture type, and operation type. Fisher's Exact Test was used to evaluate whether warfarin or NOAC therapy delayed surgery beyond 36 or 48 hours, or decreased 30-day, 6-month, or 12-month survival.

Results

Time to surgery was delayed in anticoagulated patients (p=0.028). NOAC therapy was independently associated with increased time to surgery beyond 36 hours (p=0.001), although not beyond 48 hours (p=0.355), whereas warfarin therapy was not associated with either. Anticoagulation did not increase length of stay (p=0.331). Warfarin therapy significantly reduced 30-day survival (p=0.007), but NOAC therapy did not (p=0.244). Neither warfarin nor NOAC therapy affected further survival.

Conclusions

NOAC therapy delays time to surgery beyond the NHS England 'Best Practice Tariff' in hip fracture patients. We aim to prospectively investigate long-term outcomes.

Without a NOAC antidote, policy must change to ensure time-appropriate surgery for patients on NOACs. Preoperative involvement of the haematology team is essential.

Key words

anticoagulation; delayed surgery; hip fracture

INTRODUCTION

Hip fractures are common in the elderly and, in the UK alone, 65,000 patients aged 60 and over sustained a hip fracture during 2015 (1). The incidence of hip fractures has increased over the last half-century, and projections indicate that this will continue and become a major demand on healthcare resources (2). Total UK annual hospital costs associated with hip fractures were recently estimated at more than £1 billion (3). Length of stay is a major factor in the economic burden of this public health problem (1,3).

In 2016, the National Institute for Health and Care Excellence (NICE) recommended that *'Adults with hip fracture have surgery on a planned trauma list on the day of, or the day after, admission'* (4). Operative delay beyond 48 hours has been shown to increase 30-day all-cause mortality of hip fracture patients by 41% (5).There is also a financial incentive for National Health Service (NHS) Trusts to operate on hip fractures within 36 hours by way of the NHS England 'Best Practice Tariff' (BPT) introduced in 2010. In 2016, 18.7% of patients did not achieve best practice care based on a delayed time to theatre of more than 36 hours alone (1).

Hip fractures are more common in multimorbid elderly patients, and they often have poor clinical outcomes with 1-year mortality rates approaching 36% (6). A recent study found that mortality is almost doubled for 8 years or more following the injury (7). A major cause of operative delay is anticoagulation, which many elderly patients require for cardiovascular comorbidities.

Anticoagulation with warfarin, a vitamin K antagonist (VKA), for atrial fibrillation (AF) or thromboembolic disease commonly causes this coagulopathy (8). This produces a raised international normalized ratio (INR) (9,10). Non-vitamin K antagonist oral anticoagulants (NOACs) have been recommended as alternatives to warfarin for stroke prevention in patients with non-valvular AF in several guidelines (11). NOACs act either as direct thrombin inhibitors (e.g. dabigatran) or direct factor Xa inhibitors (e.g. rivaroxaban or apixaban) thus prolonging the prothrombin time (PT). PT values (in seconds) cannot be converted to INR for NOACs because this has only been validated for VKAs (12).

It was the suspicion of the clinicians in our trust that NOACs caused more operative delay since these drugs are irreversible (12,13). This has been reported rarely in the literature, with only a case report (14) and a small case-control study (10). We therefore decided to evaluate whether patients admitted with hip fractures on NOAC therapy were at risk of operative delay, prolonged length of hospital stay, or increased mortality.

METHODS

This retrospective cohort study is reported in accordance with the STROBE statement. Data for 845 consecutive patients admitted to a level 1 trauma centre with fracture of the femoral neck between October 2014 and December 2016 were extracted from the National Hip Fracture Database and collected from electronic patient records. One patient received no surgical treatment and was excluded from analysis (Figure 1). 83 of 844 surgically treated patients (9.8%) were receiving warfarin therapy on admission, and 32 of 844 surgically treated patients (3.8%) were

receiving NOAC therapy on admission (rivaroxaban (n = 19), apixaban (n = 8), and dabigatran (n = 5)) (Table 1). Warfarin and NOAC treatment status were collected from digital patient records manually. Internally verified data were collected on the age, sex, admission Abbreviated Mental Test Score (AMTS), pre-fracture mobility as assessed for the National Hip Fracture Audit, American Society of Anesthesiologists (ASA) score, fracture type (intracapsular – undisplaced, intracapsular – displaced, intertrochanteric, subtrochanteric), operation type (internal fixation, hemiarthroplasty, total hip arthroplasty, or other), time to surgery, length of stay, and 30-day, 6-month, and 12-month survival (Table 1).

Statistical Analysis

Descriptive and demographic analysis was first performed using Microsoft® Excel (15). Variables including age, sex, admission AMTS, pre-fracture mobility, ASA score, fracture type, and operation type were analysed in a multivariable linear regression analysis to test the association between warfarin and NOAC therapy on time to surgery and length of stay. A Fisher's Exact Test was used to evaluate whether warfarin or NOAC therapy independently delayed surgery beyond 36 or 48 hours, and whether either therapy decreased 30-day, 6-month, or 12-month survival. Another Fisher's Exact Test was used in a subgroup analysis to determine if any NOAC (rivaroxaban, apixaban, or dabigatran) was associated with delayed surgery beyond 36 or 48 hours. All statistical analyses were performed using IBM® SPSS® Statistics (16).

This project was approved by and registered with the clinical audit team in our centre. The National Hip Fracture Database is a national audit in the UK approved by

the National Health Service (NHS) England Health Research Authority (HRA) Confidentiality Advisory Group.

RESULTS

Time to Surgery

After controlling for age, sex, admission AMTS, pre-fracture mobility, ASA score, fracture type, and operation type, patients on anticoagulation therapy were found to go to theatre significantly later than those not anticoagulated (p=0.028) (Table 2a). As shown in Table 1, median time to surgery for patients on warfarin therapy was 27 hours (IQR 13 hours), for patients on NOAC therapy was 29 hours (IQR 20 hours), and for patients on no anticoagulation therapy was 22 hours (IQR 10 hours). Fisher's Exact Test then showed that NOAC therapy was independently associated with increased time to surgery beyond 36 hours (p=0.001), but not beyond 48 hours (p=0.355), whereas warfarin therapy was not associated with a delay beyond 36 hours (p=0.089) or 48 hours (p=0.370) (Table 3).

The subgroup analysis is also summarised in Table 3. Rivaroxaban therapy was not associated with a delay beyond 36 hours (p=0.207), however apixaban (p=0.050) and dabigatran (p=0.003) were. None were associated with a delay beyond 48 hours (Table 3).

Length of stay

The results of the multivariable linear regression analysis model when applied to length of stay are displayed in Table 2b. This shows no association between anticoagulation therapy and length of stay (p=0.331). The variables that significantly correlated with increased length of stay were admission AMTS, pre-fracture mobility, and ASA score (Table 2b).

Survival

In view of the recent study extending to December 2016, 6-month survival data was unavailable for 170 patients (20%), and 12-month survival data was unavailable for 391 patients (46%). Warfarin or NOAC therapy were tested independently against patient survival to 30 days, 6 months, and 12 months. Warfarin therapy was associated with a significant reduction in 30-day survival (p=0.007), but there was no association with warfarin therapy and longer-term survival, or with NOAC therapy and survival.

DISCUSSION

Fractures of the neck of the femur are an ever-growing public health problem. Most often, these injuries befall the elderly, and so patients often present with multiple co-morbidities that may require anticoagulation therapy. This anticoagulation may take the form of warfarin, or one of the newer non-vitamin K antagonist oral anticoagulants (NOACs). These all reduce the physiological capacity to stop bleeding and increase surgical risks; surgical interventions should not be performed unless they have been demonstrably counteracted, or sufficient time has passed for them to be cleared from the body. The effects of warfarin can be easily offset by giving the patient vitamin K, however the NOACs do not have antidotes that are readily available within the NHS and so they must be given enough time to clear. Dabigatran has a half-life of 14-18 hours depending on the degree of renal impairment, and so 2-4 days off this drug is thought necessary before high-bleeding risk procedures, whereas rivaroxaban and apixaban have much shorter half-lives of 7-9 hours, and so need only be discontinued 24 hours before surgery (17). Local guidelines help the medical team balance the renal function of the patient with the estimated clearance of the drug, and therefore determine how long before surgery anticoagulant therapy should be interrupted. These drugs all have the potential to delay time to theatre and therefore delay the treatment that these surgical patients require, subsequently affecting outcomes. We found that patients in our cohort taking NOACs on admission were more likely to have delayed surgery.

NOACs have been shown to have better bleeding profiles than warfarin for patients with atrial fibrillation and they obviate the need for routine blood monitoring (18). According to in vitro and animal studies, NOACs may also reduce the risk of

osteoporosis posed by vitamin K antagonist anticoagulants (19). These drugs, including warfarin, interfere with γ-carboxyglutamate formation by inhibiting the carboxylation of glutamate residues of proteins that are synthesized in bone, purportedly increasing the risk of osteoporosis, and by extension a fragility fracture (19,20). NOACs do not act on this pathway and so cannot pose such risks. These novel NOACs are therefore good medical drugs in an elderly population at risk from fragility fractures, but poor surgical drugs.

We found that, when controlling for age, sex, admission AMTS, pre-fracture mobility, ASA score, fracture type, and operation type, patients on anticoagulation therapy went to theatre significantly later than those not. This delay has been reported several times before in the literature (9,10,21–23). However, to our knowledge, this study is the first to investigate the effect of three different NOACs on delayed time to surgery, and therefore should highlight which of these drugs are causing difficulty in the perioperative context. In this study, dabigatran and apixaban were particularly culpable and this could be explained by the longer half-life of dabigatran, or by the unfamiliarity of these drugs among surgeons managing hip fracture patients.

We found no association between anticoagulation therapy and length of stay. Studies reported in the literature have yielded mixed results on this issue. While Ranhoff et al. (22) and more recently Lawrence et al. (23) found that patients receiving warfarin on admission to hospital had longer lengths of stay, Eardley et al. (9) found similar results to us in a study of 1024 patients.

We found a reduced 30-day survival among patients taking warfarin, but not those taking NOACs. Reduced survival of hip fracture patients admitted on warfarin therapy has recently been reported (23). The lack of association with NOAC therapy may in part be due to the low patient numbers in our study. Regardless, clinicians involved in the operative work-up and post-operative care should be aware of a possible association between anticoagulation therapy and increased mortality in patients admitted with a hip fracture, and work together to manage such patients with care.

The ability to reverse NOACs in patients presenting with a fracture requiring surgical intervention is a pressing need. Infusion with prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP) have been used in mouse models to reverse the effects of dabigatran, but despite some success, have not shown ultimately convincing results (24). PCC has also been trialled in humans with some success although this does not represent an ideal solution in the clinical situation (25). Dialysis is possible in dabigatran, but not factor Xa inhibitors since their plasma protein binding is too high (26). Again, this does not represent a viable clinical option for a multimorbid and ageing surgical population. Specific antidotes including monoclonal antibodies are being produced and trialled but nothing is currently available within the NHS as yet (26).

There were several limitations to our study. Although our centre is unique in the UK with a fully computerised patient records (Epic Systems Corporation, Verona, WI) allowing retrospective chart reviews (27,28), the retrospective data collection could not account for some variables in our analysis such as other comorbidities, and

precise details of when anticoagulation therapy was halted over the perioperative period. This slightly pragmatic snapshot, however, reflects the reality of surgical practice. Further, we could not clearly delineate why surgery was delayed in each case. According to the 2016 National Hip Fracture Database (NHFD) report, 18.7% of patients failed to achieve best practice care because of delays to theatre, and half of these (nearly 6,000 patients) were delayed for administrative reasons (1). Another reason pertinent to our trauma centre could be the competition for theatre time which has significantly increased, delaying surgical management of hip fracture patients, since becoming a major trauma centre, with associated increases in morbidity and mortality (29).

This study reports the most patients on NOACs hospitalized with hip fractures in the literature to date, with only a case report (14); and a case-control study by Tran et al. noting similar findings (10).The number of patients evaluated in our study however was not sufficient for a thorough subgroup analysis. Despite the relatively large overall cohort, only 83 patients were on warfarin, and 32 were on NOACs. This could explain why we did not find significance in the delay to surgery among the patient group on warfarin which has been reported by many others (9,21–23,30). However, this could also stem from a change in the process of warfarin reversal at our centre. If at first vitamin K administration does not sufficiently reduce the INR, then patients are given prothrombin complex concentrate in the form of Beriplex or Octaplex to instantly reverse the effect of warfarin.

The UK Best Practice Tariff (BPT) may put pressure on surgical teams to get patients to theatre quickly in order to avoid any financial penalty. Many

anticoagulated patients cannot meet ‘best practice’ without incurring the risks of surgery with a high likelihood of bleeding because this does not allow sufficient time for these novel anticoagulant drugs to be cleared from the body. Such was the case in our cohort. It is therefore important to note that there is a potential financial implication in the safe and timely management of these patients. Until an antidote becomes widely available within the NHS, the National Institute for Health and Care Excellence (NICE) must update its guidance to appreciate the increasing number of patients on NOACs presenting with neck of femur fractures who require delayed surgery that is safe and does not promote excessive haemodynamic risk.

There are clearly an increasing number of frail and elderly hip fracture patients who are presenting to our trauma centres on anticoagulant therapy. To prepare for the medical complexity of this growing public health burden, it is crucial that orthopaedic surgeons and orthogeriatricians in the multi-disciplinary team familiarise themselves with these NOACs. These drugs show differing pharmacological characteristics, crucially different half-lives, and it is important that the team is aware of these differences in order to provide surgery that is timely but patient-centred and crucially, safe.

ACKNOWLEDGEMENTS

No acknowledgements

REFERENCES

1. National Hip Fracture Database annual report 2016 | RCP London [Internet]. [cited 2017 Jan 19]. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-hip-fracture-database-annual-report-2016

2. White SM, Griffiths R. Projected incidence of proximal femoral fracture in England: A report from the NHS Hip Fracture Anaesthesia Network (HIPFAN). Injury. 2011 Nov;42(11):1230–3.

3. Leal J, Gray AM, Prieto-Alhambra D, Arden NK, Cooper C, Javaid MK, et al. Impact of hip fracture on hospital care costs: a population-based study. Osteoporos Int. 2016;27:549–58.

4. Hip fracture in adults | quality-statement-2-timing-and-expertise-for-surgery | Guidance and guidelines | NICE [Internet]. [cited 2017 Jan 19]. Available from: https://www.nice.org.uk/guidance/qs16/chapter/quality-statement-2-timing-and-expertise-for-surgery

5. Shiga T, Wajima Z, Ohe Y. Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression. Can J Anesth. 2008 Mar 1;55(3):146.

6. Abrahamsen B, Staa T van, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009 Oct 1;20(10):1633–50.

7. Katsoulis M, Benetou V, Karapetyan T, Feskanich D, Grodstein F, Pettersson-Kymmer U, et al. Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project. J Intern Med. 2017 Jan 1;n/a-n/a.

8. Gleason LJ, Mendelson DA, Kates SL, Friedman SM. Anticoagulation Management in Individuals with Hip Fracture. J Am Geriatr Soc. 2014 Jan 1;62(1):159–64.

9. Eardley WGP, Macleod KE, Freeman H, Tate A. 'Tiers of Delay'. Geriatr Orthop Surg Rehabil. 2014 Sep;5(3):103–8.

10. Tran T, Delluc A, de Wit C, Petrcich W, Le Gal G, Carrier M. The impact of oral anticoagulation on time to surgery in patients hospitalized with hip fracture. Thromb Res. 2015 Nov;136(5):962–5.

11. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr. JC, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014 Dec 2;64(21):e1–76.

12. Kazmi RS, Lwaleed BA. New anticoagulants: how to deal with treatment failure and bleeding complications. Br J Clin Pharmacol. 2011 Oct;72(4):593–603.

13. Ahrens I, Lip GYH, Peter K. New oral anticoagulant drugs in cardiovascular disease. Thromb Haemost. 2010;104(1):49–60.

14. Rasmussen LE, Viberg BL, Pottegård A. [Fatal outcome for a patient in treatment with dabigatran suffering a subtrochanteric femoral fracture]. Ugeskr Laeger. 2015 Apr 6;177(15):V11140612.

15. Microsoft Excel 2016, Download Spreadsheet software | XLS XLSX [Internet]. [cited 2017 Feb 13]. Available from: https://products.office.com/en-gb/excel

16. IBM SPSS Statistics [Internet]. [cited 2017 Feb 13]. Available from: https://www.ibm.com/uk-en/marketplace/statistical-analysis-and-reporting

17. Vílchez JA, Gallego P, Lip GYH. Safety of new oral anticoagulant drugs: a perspective. Ther Adv Drug Saf. 2014 Feb;5(1):8–20.

18. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? J Thorac Dis. 2015 Feb;7(2):165–71.

19. Tufano A, Coppola A, Contaldi P, Franchini M, Minno GD. Oral Anticoagulant Drugs and the Risk of Osteoporosis: New Anticoagulants Better than Old? Semin Thromb Hemost. 2015 Jun;41(04):382–8.

20. Rezaieyazdi Z, Falsoleiman H, Khajehdaluee M, Saghafi M, Mokhtari-Amirmajdi E. Reduced bone density in patients on long-term warfarin. Int J Rheum Dis. 2009 Jul;12(2):130–5.

21. Diament M, MacLeod K, O'Hare J, Tate A, Eardley W. 'Early Trigger' Intravenous Vitamin K: Optimizing Target-Driven Care in Warfarinised Patients With Hip Fracture. Geriatr Orthop Surg Rehabil. 2015 Dec;6(4):263–8.

22. Ranhoff AH, Martinsen MI, Holvik K, Solheim LF. Use of warfarin is associated with delay in surgery for hip fracture in older patients. Hosp Pract 1995. 2011 Feb;39(1):37–40.

23. Lawrence JE, Fountain DM, Cundall-Curry DJ, Carrothers AD. Do Patients Taking Warfarin Experience Delays to Theatre, Longer Hospital Stay, and Poorer Survival After Hip Fracture? Clin Orthop. 2017 Jan;475(1):273–9.

24. Zhou W, Schwarting S, Illanes S, Liesz A, Middelhoff M, Zorn M, et al. Hemostatic Therapy in Experimental Intracerebral Hemorrhage Associated With the Direct Thrombin Inhibitor Dabigatran. Stroke. 2011 Dec 1;42(12):3594–9.

25. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011 Oct 4;124(14):1573–9.

26. Yates SW. Interrupting Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. Pharm Ther. 2014 Dec;39(12):858–80.

27. McIndoe R. Time to tear ourselves away from paper. Health Serv J. 2007 Mar 8;117(6046):18–9.

28. Scott PJ, Curley PJ, Williams PB, Linehan IP, Shaha SH. Measuring the operational impact of digitized hospital records: a mixed methods study. BMC Med Inform Decis Mak. 2016;16:143.

29. Barr LV, Vindlacheruvu M, Gooding CR. The effect of becoming a major trauma centre on outcomes for elderly hip fracture patients. Injury. 2015 Feb;46(2):384–7.

30. Tal A, Rubin G, Rozen N. Treatment with vitamin K in hip fracture patients receiving warfarin. Isr Med Assoc J IMAJ. 2013 Jul;15(7):348–51.

TABLES

Table I

Table 1. Sample description for patients not taking anticoagulation therapy, and those on warfarin or NOAC therapy				
Measure	**No anticoagulation**	**On warfarin**	**On NOAC**	**Total**
Number of patients (%)	729 (86)	83 (10)	32 (4)	844 (100)
Age, years (median, IQR)	85 (12)	84 (10)	87 (11)	85 (12)
Female, number (%)	535 (73)	57 (69)	26 (81)	618 (73)
AMTS, median (IQR)	9 (6)	10 (3)	8 (5)	7 (4-10)
Fracture type, number (%)				
Intracapsular - undisplaced	11 (2)	0 (0)	1 (3)	12 (1)
Intracapsular - displaced	386 (53)	54 (65)	19 (59)	459 (54)
Intertrochanteric	275 (38)	23 (28)	9 (28)	307 (36)
Subtrochanteric	57 (8)	6 (7)	3 (9)	66 (8)
ASA score, number (%)[a]				
5	2 (0)	0 (0)	0 (0)	2 (0)
4	78 (12)	9 (14)	7 (23)	94 (13)
3	299 (48)	44 (67)	20 (65)	363 (50)
2	175 (28)	8 (12)	2 (6)	185 (26)
1	71 (11)	5 (8)	2 (6)	78 (11)
Operation type, number (%)				
Internal fixation	374 (51)	31 (37)	12 (38)	417 (49)
Hemiarthroplasty	313 (43)	50 (60)	19 (59)	382 (45)
THA	39 (5)	2 (2)	0 (0)	41 (5)
Other	3 (0)	0 (0)	1 (3)	4 (0)
Time to surgery				
Median hours (IQR)	22 (10)	27 (13)	29 (20)	22 (11)
<36 hours, number (%)	618 (85)	64 (77)	19 (59)	701 (83)
<48 hours, number (%)[b]	682 (94)	79 (95)	29 (91)	790 (94)
Length of stay, median days (IQR)[c]	12 (11)	12 (7)	14 (9)	12 (10)
Survival, number (%)				
30-day	697 (96)	73 (88)	30 (94)	800 (95)
6-month[d]	478 (82)	55 (81)	20 (83)	553 (82)
12-month[e]	301 (76)	33 (80)	12 (71)	346 (76)
[a]ASA score missing for 122 patients; [b]includes patients operated on in <36 hours; [c]Length of stay missing for 25 patients; [d] 6-month survival missing for 170; [e] 12-month survival missing for 391				

Abbreviations:

NOAC – non-vitamin K antagonist oral anticoagulants

IQR – interquartile range

AMTS – abbreviated mental test score

ASA – American Society of Anesthesiologists

Table II

Table 2. Multivariable regression results showing factors related to (a) time to surgery (hours) (b) length of stay (days)					
(a) Time to surgery (hours)			(b) Length of stay (days)		
Factor	**Standardized Beta Coefficient**	**p value**	**Factor**	**Standardized Beta Coefficient**	**p value**
Age	-0.031	0.443	Age	0.047	0.241
Sex	0.078	0.036*	Sex	0.050	0.168
AMTS	0.003	0.950	AMTS	-0.170	0.000*
Pre-fracture mobility	0.049	0.262	Pre-fracture mobility	-0.109	0.011*
ASA score	0.060	0.127	ASA score	0.127	0.001*
Fracture type	0.063	0.199	Fracture type	0.017	0.724
Operation type	0.128	0.010*	Operation type	-0.037	0.434
Anticoagulation	0.083	0.028*	Anticoagulation	0.230	0.331

Abbreviations:

AMTS – abbreviated mental test score

ASA – American Society of Anesthesiologists

Table III

Table 3. Fisher's Exact Test results to show if warfarin or NOAC therapy was associated with delayed surgery beyond 36 or 48 hours		
Survival	**Anticoagulation therapy**	**p value (1-sided test)**
Delayed >36 hours	Warfarin	0.089
	NOAC	0.001*
	- Rivaroxaban	0.207
	- Apixaban	0.050*
	- Dabigatran	0.003*
Delayed >48 hours	Warfarin	0.370
	NOAC	0.355
	- Rivaroxaban	0.281
	- Apixaban	0.108
	- Dabigatran	0.282

Abbreviations:

NOAC – non-vitamin K antagonist oral anticoagulants

FIGURE LEGENDS

Figure 1. Flow diagram showing selection of patient data